Supplemental Material for Online Only

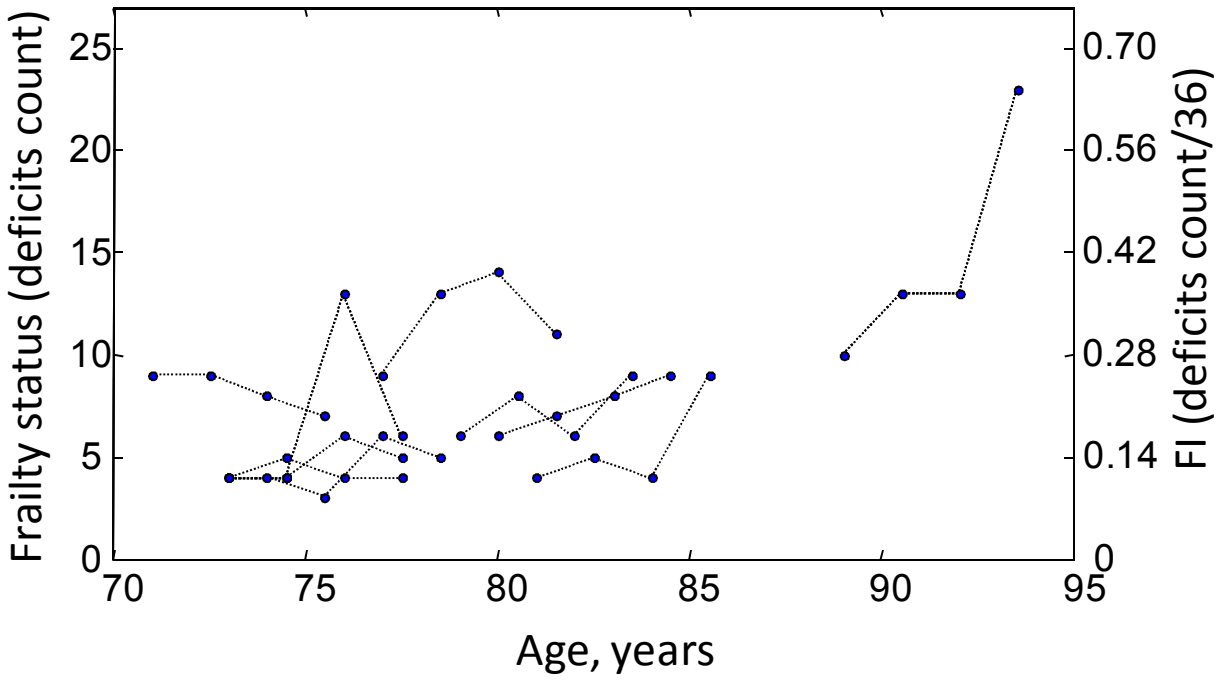
Appendix:

1. Individual trajectories of frailty.

The health of an individual changes over time, as reflected in varying vulnerability to adverse outcomes, and thus varying frailty status. Frailty status can be operationalized in a deficit count, and over time, not just deficit accumulation, but deficit diminution (i.e. improvement) can be observed. Figure S1 illustrates a variety of changes in frailty status, here represented both by the number of deficits (left axis) and by the frailty index (right axis) in ten randomly selected individuals from the PEP dataset. Note that there is often fluctuation, and that changes in frailty status occur in both directions: i.e., it is not just a matter of decline, even though, on average, decline predominates. Clearly, individual courses can show a highly irregular pattern, including a few cases of "big jumps" against a background of relatively small changes. Processes that show such irregular behaviour on an individual basis, which are nevertheless summarizable at a group level, are typically referred to as "stochastic" processes, rather than purely "random", so that the model employed here is a stochastic model of changes in frailty states in relation to aging. In other words, the outcomes at each transition step can be generally represented by the distribution of changes. The mean change is an important characteristic of this distribution, but it gives only the average outcome, which, in a sense, ignores the rest of the information about all possible outcomes; these other outcomes – and not just the mean value - are represented by the model. When the distribution of the outcomes is expressed as counts, it can be represented by a simple Poisson law which has only one parameter (the Poisson mean). We have demonstrated that frailty status (when expressed via the deficits count) shows the Poisson distribution [10-12,22,23] with a very high precision (the goodness of fit typically extended 90% of "explained" variability).

Examples of the Poisson distribution with different values of the Poisson mean are shown in Figure S2.

Figure S1. Examples of frailty trajectories for ten randomly selected participants between baseline and the subsequent follow-up assessments. The vertical axis is the frailty status, represented by the deficit count (on the left axis) and by the frailty index on the right axis.



2. The multistate transition model.

Consider that, having started with n deficits at baseline, survivors have k deficits at follow-up. At follow-up, k can be equal n (i.e., the same number of deficits, representing stability in the frailty state) or k can be greater than n (representing more deficits and worsening) or k can be less than n (improvement). The stochastic model of frailty state transitions is a multistate transition model allowing the calculation of the probabilities of changes in all directions (i.e. all values of k at follow-up) from any baseline state of n deficits. [10-12,22,23] Thus from any individual's initial frailty state 'n', P_{nk} is the probability that this individual will have frailty

state '*k*' at the next assessment. The transition probabilities for survivors typically can be represented by a Poisson distribution: [10-12]

$$P_{nk} = \frac{\rho_n^k}{k\,!} e^{-\rho_n} \qquad (1)$$

The parameter ρ_n can depend on the current state *n* and covariates such as age, sex and mobility. Formally, considering a set of *m* covariates $z_{j,}$ *(j=0,...m;* z_0*=1;* z_1*=n)* the Poisson parameter ρ_n can be represented as follows:

$$\rho_n = \sum_{j=0}^{m} \beta_j z_j \qquad (2)$$

Likewise, the probability of death can also be parameterized as follows:

$$logit(P_{nd}) = \sum_{j=0}^{m} b_j z_j \qquad (3)$$

where the parameters β_j and b_j are the regression coefficients of *j*-th covariate in the Poisson mean and the logit probability of death, respectively. The parameters in equation 2 can be estimated using a Poisson regression and the parameters characterising mortality (3) can be estimated with the binary logistic regression. These procedures are available in virtually all statistical software and do not require special statistical programming to be used.

3. Estimation of the binary covariates.

Table S1,A. Parameter estimates and their 95% confidence intervals for Poisson regression

Covariate	Regression coefficient for Poisson model in survivors		
	18-month follow-up	36-month follow-up	54-month follow-up
(Intercept)	0.96 (0.64, 1.28)	1.47 (1.09, 1.85)	1.68 (1.26, 2.08)
Frailty Index count at baseline	0.84 (0.78, 0.91)	0.89 (0.82, 0.97)	0.88 (0.81, 0.97)
Age	0.68 (0.31, 1.05)	0.98 (0.55, 1.41)	1.81 (1.35, 2.28)
Sex	0.15 (-0.21, 0.51)*	0.29 (-0.12, 0.71)*	-0.28 (-0.72, 0.15)*
Mobility	0.66 (0.21, 1.12)	0.92 (0.39, 1.45)	0.88 (0.31, 1.46)

Table S1,B. Parameter estimates and their 95% confidence intervals for logistic regression

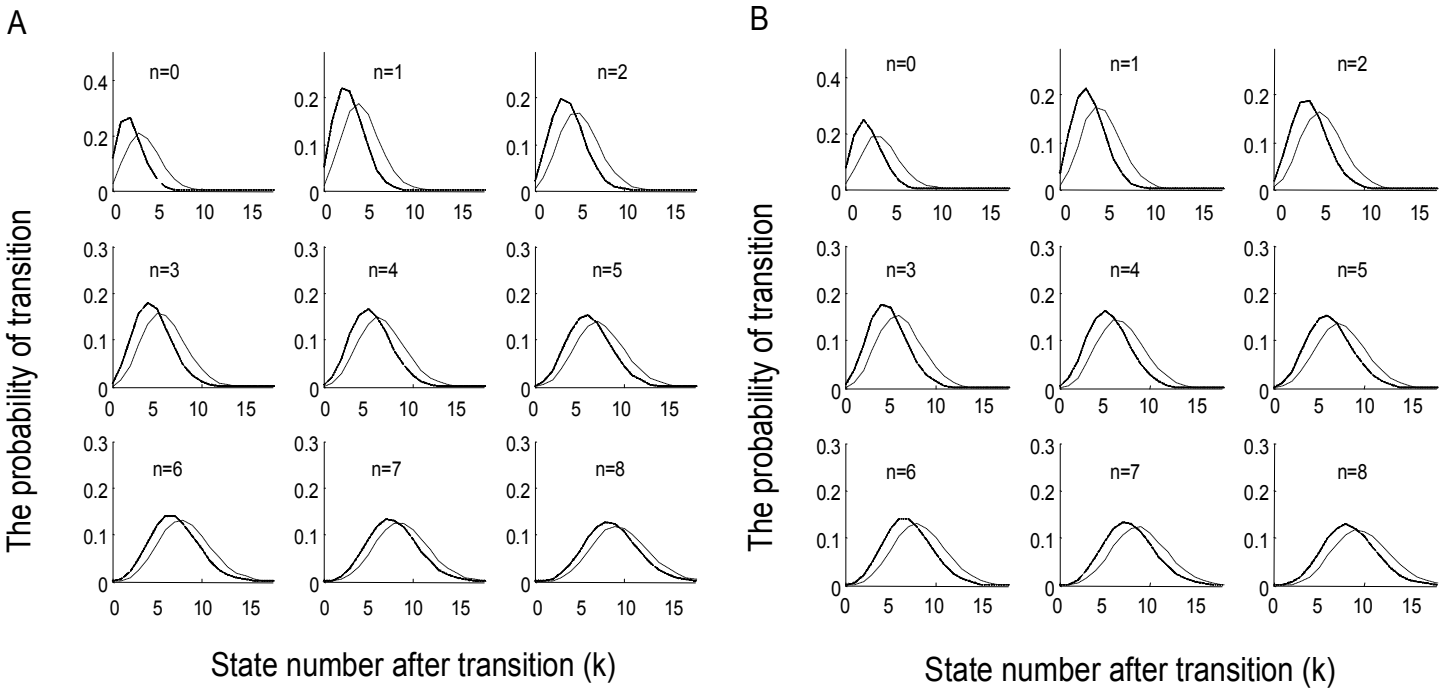
Covariate	Regression coefficients for logistic regression for mortality		
	18-month follow-up	36-month follow-up	54-month follow-up
(Intercept)	-4.32 (-5.51,-3.51)	-3.64 (-4.25,-3.02)	-3.21 (-3.73, -2.69)
Frailty Index count at baseline	0.14 (0.06, 0.21)	0.15 (0.08, 0.21)	0.17 (0.12, 0.22)
Age	0.48 (-0.17, 1.13)	0.55 (0.07, 1.04)	0.54 (0.14, 0.94)
Sex	0.82 (0.19, 1.43)	0.86 (0.39, 1.33)	0.82 (0.42, 1.22)
Mobility	0.10 (-0.61, 0.81)*	0.08 (-0.61, 0.44)*	0.27 (-0.16, 0.71)*

* indicates statistically insignificant estimates ($p>0.05$)

4. Transition probabilities calculated from the model.

The density distributions of all transitions between the different states showed some similarities between the effects of age (Figure S2, Panel A) and mobility (Figure S2, Panel B). In all panels, there is an evident shift to the right of the curves represented by older participants (Panel A, solid curves) and participants with poor mobility (Panel B. solid curves).

Figure S2. The probability of transition in frailty states represented by age groups in Panel A (dichotomised at 78 years)) and by mobility groups in Panel B (dichotomised at walking speed of 10 sec for rapid gait test). Each horizontal axis represents the frailty state at follow-up from a given baseline frailty state *n* (shown in each subplot) to the *k* state at follow-up (horizontal axis). Solid lines indicate the transition probabilities for the younger group (Panel A) and good mobility (Panel B), and dashed lines indicate the transition probabilities for the older group and poor mobility, respectively



5. Parameter estimates for the mortality model when baseline frailty status is not included.

Table S2. Parameter estimates and their 95% confidence intervals in logistic regression. Covariates exclude frailty at baseline.

Covariate	The regression coefficients for logistic regression		
	18-month follow-up	36-month follow-up	54-month follow-up
(Intercept)	-3.92 (-4.68,-3.15)	-3.44 (-4.05,-2.83)	-3.45 (-4.05, -2.84)
Age	0.09 (0.03, 0.14)	0.08 (0.04, 0.12)	0.08 (0.04, 0.12)
Sex	0.63 (0.04, 1.22)	0.75 (0.31, 1.21)	0.74 (0.35, 1.12)
Mobility	0.01 (-0.02, 0.05)*	0.04 (0.01, 0.08)	0.11 (0.06, 0.15)

* indicates insignificant estimates ($p>0.5$)

In this table, mobility is associated with mortality for 36 and 54 months follow-up. This is not the case, however, if baseline frailty is added to covariates (Table 2B, in the main body of the paper).